IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kai LICHA et al. Examiner: KOSAR, Andrew D.

Serial No.: 10/762,582 Group Art Unit: 1654

Filed: January 23, 2004

Title: HYDROPHILIC, THIOL-REACTIVE CYANINE DYES AND CONJUGATES THEREOF WITH BIOMOLECULES FOR FLUORESCENCE DIAGNOSIS

REPLY BRIEF

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Sir:

Further to the Examiner's Answer mailed on May 30, 2008, please consider the following.

The Rejection Under 35 USC 103

The Examiner's Answer on pages 18 and 19 newly alleges that "it should be noted that *KSR* forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness."

The decisions of the Federal Circuit in *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007), and *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. et al.*, 2007-1397, -1398 (Fed. Cir. 2008), the latter having been recently decided, i.e., 9 days before the filing of this Reply Brief, are highly relevant to the allegations. Both of these controlling decisions post date *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007) and specifically discuss the requirements of establishing obviousness, especially in the chemical arts.

One of the issues in *Takeda* was whether picking a specific compound as a starting point (lead compound) from the prior art disclosing it and several others is obvious without a reason leading to its choice. The Federal Circuit's answer was no.

The prior art reference in *Takeda* taught the exact same use for the compounds as claimed in the later application (antidiabetic treatment), taught 34 compounds specifically

from a broad generically disclosed formula, including the specific compound of interest in the later application, the prosecution history of the prior art reference supplied test data for nine specific compounds, including the specific compound of interest, the compound of interest was specifically claimed in one of the patents in the prior art patent family, i.e., a claim specifically was directed to the compound of interest alone (see claim 4 of US 4,444,779), and the prosecution history thereof included a statement to the effect that the claimed compounds became important, especially the compound of interest.

A separate prior art document tested 101 various prior art compounds, including the compound of interest, and indicated some side effects associated with the compound of interest.

The lower court held, which holding was upheld by the Federal Circuit, that the selection of the compound of interest as a lead compound was not obvious in view of the prior art. The lower court held that any "suggestion to select" the compound of interest was negated by the separate prior art document testing various prior art compounds. (Emphasis added.) The Federal Circuit rejected arguments relying on *KSR* that "the claimed compounds would have been obvious because the prior art compound fell within 'the objective reach of the claims.'"

Thus, it is clear that the law requires "suggestion to select" the compounds of interest from the prior art, and it is not adequate that a compound merely fall within the objective reach of a claim.

The Federal Circuit in *Eisai* characterized the holding of Takeda by stating that "obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound." Emphasis added.

The court went on to summarize the state of the law of obviousness, especially as it pertains to chemical arts, as follows:

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might **identify a problem and pursue potential solutions**. Second, KSR presupposes that the record up to the time of invention would **give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound**. See Takeda, 492, F.3d at 1357 ("Thus, ***in cases involving new chemical***

> ***compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness*** of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would **supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions**," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that **this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness**." **To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable**. (Emphasis added.)

The compound of the claims in *Eisai*, i.e., Lansoprazole, was in an art where the core of the compound was known and described in a class of compounds by a reference, i.e., Brändström. Rabeprazole, a specific prior art compound, had the same core and substituents thereon with the exception of an $OCH_2CH_2CH_2OCH_3$ group in the 4-position, where the claimed Lansoprazole has an OCH_2CF_3 group. Omeprazole, another compound sharing the same core has an OCH_3 group in the 4-position. The Federal Circuit even taking the evidence most favorable to the movant on Summary Judgment challenging the validity of the patent did not find obviousness. There was evidence in the record that the fluorinated substituent on the lead, i.e., Lansoprazole, which was selected as the allegedly obvious lead by the movant, provided a special path to achieving lipophilicity. Without discernible reason on the record why one of ordinary skill in the art would have modified this group, which was known to provide lipophilicity, the Federal Circuit held that there was no obviousness.

In the present case Zaheer teaches the conjugation of cancer specific ligands to NIR fluorophores. See abstract. Zaheer teaches the preparation of the conjugates by reacting IRDye78-NHS with various ligands. See the reaction schemes on page 357, in figure 1A. Zaheer cautions that there are various difficulties, identified as "five caveats" on page 362, first column, line 2 from the bottom of the page, and set forth thereafter up to nearly the end of page 363, which difficulties include the following: the ligands with more than one primary amine must be used with caution, the ratio of fluorphore to ligand must be determined empirically and even thereafter "it will likely be extremely difficult to purify to homogeneity molecules with IRDye78 conjugated to a particular primary amine," caution advised when using strong nucleophiles, e.g., thiol groups and imidazole groups, as they are capable of

attacking the NHS ester of IRDye78-NHS, and because "nucleophiles can displace the entire phenoxy/ligand group resulting in decoupling of fluorphore and ligand," difficulties arising in purification, e.g., by using HPLC, as some conjugates adhere to metal surfaces, including HPLC tubing, indication that charged molecules, such as peptides, will tend to elude with multiple peaks when using ion-pairing HPLC at neutral pH, that the final sample concentration and storage can have profound effects on the stability of IRDye78 conjugates, and that for in vivo applications, care must be taken that the conjugate does not self-aggregate, etc. Zaheer summarizes all this at the end of the reference on page 364, column 1, line 4, as follows: "Working with this fluorophore requires attention to detail with respect to the choice of ligand, the conjugation reaction, the purification strategy, and the formulation for in vivo use."

Despite all this, the Office Action alleges that it would have been obvious to use this specific compound as the lead for modifications, i.e., two modifications, the changing of the ligand to the linker of a secondary reference, which linker was a linker for a completely different compound for a different use, i.e., radiolabeling, and the changing of the two propyl sulfonate groups to two ethyl sulfonate groups.

Applicants respectfully disagree with the allegation that one of ordinary skill in the art would have found it obvious to select this specific compound from the prior art for modifications in view of the long list of caveats of use provided by Zaheer. As the record establishes, there are numerous compounds in the prior art with alleged similar cores. See, e.g., the Examiner's Answer on page 19, last line to almost the end of page 20. Nevertheless, even assuming that one would select this compound, as the Examiner did, as the lead for modifications, there is not an adequate amount of reason or motivation given to one of ordinary skill in the art for the specific modifications needed to achieve the claimed compounds.

The Office Action cites Chorev as allegedly providing the linker needed to achieve the linker of the compounds of the present claims. The alleged motivation (see, e.g., page 5 of the Examiner's Answer) is that Chorev teaches "the high specificity of the maleimido moiety towards a sulfhydryl group which results in an efficient moiety towards a sylfhydryl group which results in an efficient and quantitaive addition of thiols across the activated double bond of the maleimido moiety to form a stable thio-ether." See Chorev column 2, lines 14-18. Chorev then continues at the end of the same paragraph, on column 2, lines 28-30, that the compounds disclosed therein are thus useful for the "indirect radiolabeling of peptides

containing sulfhydryl groups by using the maleimido-based reagents of this invention." (Emphasis added.) Thus, the use and alleged motivation for the selection of the maleimido moiety of Chorev as the linker is in its ability to link to peptides.

However, Zaheer teaches on page 363, second full paragraph, that "certain charged molecules, such as peptides, will tend to elute with multiple peaks when using ion-pairing HLPC at neutral pH." (Emphasis added.) See further discussion on this issue in Zaheer, e.g., on page 363. As such, the usefulness of the compounds of Zaheer are limited when it comes to the detection of peptides, which is the alleged reason for selecting the linker of Chorev, which are disclosed to be used for the labeling of peptides. Applicants submit that in view of the disclosures of these references taken together, one of ordinary skill in the art would not have found the combination obvious. There is evidence in the references that teaches away from the selection of the linker of Chorev for the fluorophores of Zaheer, which fact pattern closely parallels the fact patterns in the decisions of the Federal Circuit discussed above, i.e., *Takeda* and *Eisai*, where obviousness was not found.

Moreover, even if the alleged modifications to the linker would have been found obvious, further modifications to the two propyl sulfonate groups of Zaheer's compound would have been needed to achieve the claimed compounds. While even making a single modification is not obvious to one of ordinary skill in the art without some reason for making such a modification, when multiple modifications are at issue, the likelihood that one of ordinary skill in the art would have found it obvious to make the multiple modifications simultaneously to the compounds of Zaheer, especially without a reason provided for such modifications in the prior art, is highly unlikely.

The Enablement Rejection Under 35 USC 112

The Examiner's Answer alleges that the formation of solvates is not enabled because, e.g., the formation of solvates is unpredictable. In support, the Office Action quotes a series of passages from *Vippagunta* which indicate that certain predictions about solvates or hydrates of a compound are complex and difficult. See, e.g., the Examiner's Answer at the bottom of page 10.

However, the Office Action appears to ignore within the same document the passages which establish that the claims directed to solvates are enabled. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of

> the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling ... Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. ...
>
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true, that the prediction of what a particular solvate of a compound will actually look like, e.g., whether one, 3 ½, 6 or 12 solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

Even the very paper cited in support of the rejection demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18 of *Vippagunta*.

Additionally, based on the above discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that there is no lack of enablement.

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) holding that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought

to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case. In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates could be formed. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005).

The Written Description Rejections Under 35 USC 112

"The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." See *In re Kaslow*, 217 USPQ 1089 (CAFC 1983), citing *In re Edwards*, 558 F.2d 1349, 196 USPQ 465 (CCPA 1978) and *In re Herschler*, 591 F.2d 693, 200 USPQ 711 (CCPA 1979).
In addition to the description in the specification, one of ordinary skill in the art knows generally what a solvate is and can readily envision the types of prodrugs possible. Moreover, the types of prodrugs possible can be easily tested in a variety of tests/models to see whether the recited compounds result therefrom. See, e.g., *Vippagunta*, discussed above.

Moreover, as discussed in the Appeal Brief, the decision *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006) is highly relevant to the issues herein. Even absent specific examples of solvates, or detailed description of the structures thereof, or even absence of actual reduction to practice of solvates, in view of *Falkner*, there is not an adequate reason provided by the Office Action for the alleged lack or written description rejection, especially in view of the sate of the art.

Applicants teach in the application that the invention includes the solvates of the claimed compounds, and those of ordinary skill in the art do not have any reason to conclude that the inventors have not invented the claimed invention or were not in possession of the claimed invention at the time of the filing of the present application.

Thus, one of ordinary skill in the art would understand from the disclosure that the inventors of the present application had possession of the claimed matter, and therefore, written description thereof is present in the application.

Reversal of all the rejections is respectfully and courteously requested.

Respectfully submitted,

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